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Research Article

Response Evaluation to Oxaliplatin-Based Adjuvant Chemotherapy after Curative Resection between Right and Left-Sided Stage II and III Colon Cancer: A Retrospective Survival Analysis

Cynthia Eid Nasr*, Cassandra Nasr, Stephanie El Hawat, Christelle El Riachy, Marcel Antoine Massoud

Department of Psychology, Holy Spirit University of Kaslik, Jounieh, Lebanon

ABSTRACT

Background: Colon cancer is divided into right and left colon cancer. It manifests with distinct physiopathology, histology, presentation, and prognosis. The choice of treatment for stage IV disease is based on tumor sidedness. However, until now, stage II and III diseases are being treated with the same regimens regardless of the tumor location.

Methods: A retrospective survival analysis was performed between January 1, 2009 and December 31, 2019 on 57 Lebanese patients who were diagnosed with stage II or III colon cancer and who underwent curative surgical resection followed by Oxaliplatin-based adjuvant chemotherapy (XELOX or FOLFOX). Response to chemotherapy, as well as recurrence, were assessed with thoraco-abdominopelvic CT scan or Magnetic Resonance Imaging (MRI), scheduled regularly.

Results: Left-sided tumors were more common than right-sided ones, 57.9% *vs.* 42.1% (p=0.483).

Concerning the tumor size, Right Colon Cancer (RCC) recorded larger sizes (5.53 cm *vs.* 4.89 cm) compared to the Left Colon Cancer (LCC), but this difference is not statistically significant (p=0.252).

Despite cancer localization, FOLFOX was the main regimen used for stage III colon cancer, while XELOX was the main one for stage II.

Finally, the survival rate in the RCC group was 100% in the first year post-surgery (p=0.385), remained 100% in the second year and until the sixth year (p=0.214; p=0.005 respectively), then decreased to 95.65% in the seventh year (p=0.021). However, the survival rate in the LCC group was 96,8% in the first year post-surgery (p=0.385), then decreased gradually to 93,5% in the second year (p=0.214); it reached 71% in the fifth year (p=0.005) and remained the same in the 3 years that followed.

Conclusion: Colon cancer is a type of malignancy that carries a good prognosis when discovered at the early stages.

A better prognosis was noted in RCC compared to LCC in early-stage disease (stage II-III), with a 5-year survival rate of 100% in RCC *vs.* 71% in left sided ones.

Keywords: Colon cancer; Right; Left; Stage II; Stage III; XELOX; FOLFOX; Survival; Recurrence

Abbreviations: CC: Colon Cancer; CEA: Carcinoembryonic Antigen Level; FU: Follow Up; KM: Kaplan-Meier; LCC: Left Colon Cancer; MRI: Magnetic Resonance Imaging; OS: Overall Survival; RCC: Right Colon Cancer; TNM Classification: Tumor-Nodes-Metastases Classification

Correspondence to: Cynthia Eid Nasr, Department of Psychology, Holy Spirit University of Kaslik, Jounieh, Lebanon, Tel: 769342646; E-mail: cynthianasr1994@gmail.com

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INTRODUCTION

Colon Cancer (CC) is a common malignancy worldwide. Approximately every year, 1 million people are affected, and more than 500,000 patients die. It is the third most common cancer among men and women after prostate/breast and lung cancers, and a major factor of morbidity and mortality. CC is divided into right and left colon cancer that manifests with distinct physiopathology, histology, presentation and prognosis. Early detection and removal of neoplastic polyps can prevent the development of colon cancer [1].

Consequently, over the last two decades, the incidence of CC significantly decreased, and so did the mortality rate, owing to the use of effective screening procedures. Over the past years, the incidence of RCC is increasing.

Many factors can contribute to the development of CC. Some risk factors are modifiable, such as smoking, heavy alcohol consumption, obesity, unhealthy diet with low consumption of fruits and vegetables, while others are non-modifiable factors like aging, type two diabetes, inflammatory bowel disease, genetics and family history (e.g., familial adenomatous polyposis, Gardner's syndrome, Lynch syndrome).

In early stages, CC is usually asymptomatic. Generally, symptoms are present in advanced stages and depend on the size and the location of the tumor. Right sided colon cancer mainly causes abdominal pain and iron deficiency anemia due to occult blood loss. On the other hand, hematochezia, recent change in bowel habits (diarrhea/constipation), obstruction, and abdominal pain are usually present in left-sided colon cancer [2].

CC is suspected by colonoscopic appearance of indurated, ulcerated, friable, and irregular margin of colon lesions; it is confirmed by biopsy and histological examination of suspected lesions.

The choice of treatment in CC depends on staging. Patients with stage I and low-risk stage II CC are treated with wide surgical resection and anastomosis, while stage III and high-risk stage II CC, are treated with curative surgical resection followed by Oxaliplatin-based adjuvant chemotherapy. It is worth noting that high-risk stage II CC patients present one of these clinical features: Colon perforation or obstruction at presentation, lymph node sampling<12, poorly differentiated tumor, positive surgical margins, vasculo-lymphatic, or perineural invasion.

For surgical approach, the colectomy segment should include the tumor surrounded by normal colon for at least 5 cm on each side [3].

Based on the localization of the tumor and multiple biomarkers like MSI, KRAS, NRAS, and BRAF mutations, oncologists are able to choose the best treatment option for their patients. The most important predictive factor for prognosis is stage at diagnosis.

Concerning tumor location, the prognosis of LCC is better than the right. Moreover, compared to all colon segments, transverse cancer has the worst prognosis, while sigmoid cancer has the best. Furthermore, many studies have proved that advanced age (>70 years old), large tumor size (>5 cm), diagnosis in the setting of intestinal obstruction or perforation, poorly differentiated tumor, lympho-vascular invasion, cancer involvement at surgical margins, high serum level of Carcinoembryonic Antigen level (CEA) preoperatively (>5 ng/dl), sustained and progressive rise of CEA level postoperatively or liver metastasis at clinical presentation are poor prognostic factors for Overall Survival (OS) of colon cancer patients.

The right-left classification of colon cancer is imperative in guiding the treatment choices for stage IV disease. However, until now, stage II and III diseases are being treated with the same regimens regardless of the tumor location.

To our knowledge, Lebanon still lack studies on survival rates for stage II *vs.* III and right *vs.* left CC when treated with Oxaliplatin-based adjuvant chemotherapy. So, this study aims to evaluate differences, if present, in the response evaluation between left and right colon cancer in Lebanese patients diagnosed with either stage II or III colon cancer between 2009-2019 and treated with XELOX or FOLFOX regimen after curative resection of the tumor [4].

MATERIALS AND METHODS

This is a retrospective analysis including Lebanese patients who were diagnosed with stage II or III colon cancer and who underwent curative surgical resection followed by Oxaliplatin-based adjuvant chemotherapy (XELOX or FOLFOX). We limited the diagnosis date to the period between January 1, 2009 and December 31, 2019. Data were collected from Notre Dame Des Secours University Hospital in Jbeil [5].

For this study, the most relevant demographic and clinical variables were collected and included:

- Patient gender
- Diagnosis date
- Age at diagnosis
- Body mass index
- Predisposing conditions and family history
- Cancer detection method
- Obstruction or perforation at presentation
- Surgery type (elective or emergent)
- Tumor location (right or left colon)
- Tumor histology and grade
- Presence or not of lympho-vascular invasion
- Number of nodes examined and number of positive lymph nodes
- Tumor staging Tumor-Nodes-Metastases (TNM) classification
- Oxaliplatin-based adjuvant chemotherapy regimen chosen
- Treatment schedule and cycles
- Total dose of Oxaliplatin received
- Chemotherapy-induced toxicity and
- Post treatment follow-up.

Patients with rectal cancer, non-adenocarcinoma colon cancer histologic type, stages I and IV CC, and who received neoadjuvant chemotherapy or radiotherapy were excluded from the study.

The duration of treatment and side effects (gastro-intestinal, hematologic and neurologic) leading to dose reduction and discontinuation were noted.

In order to detect any recurrence, a regular Follow Up (FU) with thoraco-abdominopelvic CT scan or MRI must be scheduled every three months for the first year after treatment completion, then every four months the second year then every six months until the fifth year and at last yearly [6].

The OS was defined as the interval in years from the date of surgery till the date of death. The mortality rate was analyzed yearly.

The aim of this study is to evaluate the difference in recurrence and survival rate between right and left-sided stage II and III colon cancer after curative surgical resection of the tumor followed by Oxaliplatin-based adjuvant chemotherapy.

Statistical analysis

SPSS 25 version was used to perform the following statistical analyses:

- **Descriptive statistics:** Frequency tables, cross tabs, means, medians, standard deviations.
- The Kaplan-Meier (KM) method analysis which is a non-parametric method used to estimate the survival probability from observed survival times.
- The log-rank test is a hypothesis test to compare the survival distributions of two or more groups.
- The *Chi-square* test is a statistical method used to test whether two qualitative variables are independent or not.
- An independent samples t-test, to compare the means of two groups.
- A median comparison test, to compare the medians of two or more groups.
- The Kruskal-Wallis test, a non-parametric test for data of small size, was used to compare the means of 3 or more groups.

RESULTS

Sociodemographic characteristics

A group of 57 patients diagnosed with CC underwent a tumor resection procedure followed by adjuvant chemotherapy (XELOX, FOLFOX) [7].

Tables 1-3 summarize respectively the baseline characteristics, the tumor pathological characteristics, and the treatment option of the total population.

Table 1: Baseline characteristics of the total population.

	N=57 (%)
Gender	
Female	30 (52.6%)
Male	27 (47.4%)
Age at diagnosis, mean ± SD (years)	59.84 ± 11.572
Family history	4 (7%)
Tumor site	
Right	33 (42.1%)
Left	24 (57.9%)
Obstruction	
Yes	11 (19.3%)
No	46 (80.7%)
Perforation	
Yes	1 (1.8%)
No	56 (98.2%)
Surgery type	

Elective	48 (85.7%)
Emergent	8 (14.3%)

Table 2: Tumor pathological characteristics of the total population.

Staging	
Stage II	16 (28.6%)
Stage III	40 (71.5%)
Staging (pT)	
T1	1 (1.8%)
T2	1 (1.8%)
T3	22 (39.3%)
T4	32 (57.2%)
Staging (pN)	
N0	16 (28.6%)
N1	32 (57.2%)
N2	8 (14%)
Tumor grade	
Grade I	8 (14.3%)
Grade II	45 (80.4%)
Grade III	3 (5.4%)
Number of lymph nodes removed, mean ± SD	19.38 ± 10.857
Number of lymph nodes positive, mean ± SD	2.05 ± 2.022
Lympho-vascular invasion	
Yes	29 (50.9%)
No	28 (49.1%)

Table 3: Treatment options and side effects of the total population.

Adjuvant treatment	
FOLFOX	31 (54.4%)
XELOX	26 (45.6%)

Number of cycles containing Oxaliplatin, mean ± SD	9.49 ± 2.458
Serious toxicities during treatment	
Yes	30 (52.6%)
No	27 (47.4%)
Dose reduction	
Yes	15 (26.3%)
No	42 (73.7 %)
Treatment discontinuation	
Yes	7 (12.3%)
No	50 (87.7%)
Neuropathy at end of treatment	
No	35 (61.4%)
Yes	
Grade 1	9 (15.8%)
Grade 2	9 (15.8%)
Grade 3	4 (7.0%)
Recurrence	16 (28.1%)
Death	10 (17.5%)

Patients' FU revealed no recurrence of the disease in 68.4% of the population. Among the remaining patients, 3.55% were lost to follow-up and 28.1% (16 cases) had recurrence of their disease (p=0.863).

The survival rate of the total population was analyzed yearly and showed that 98.15% of patients stayed alive after one year of surgery (p=0.313). This percentage decreased to 94.44% the third year (p=0.552), to 83.33% the fifth year (p=0.715), and to 81.48% the seventh year (p=0.484) [8].

Left-sided tumors were more common than right-sided ones, 57.9% *vs.* 42.1% (p=0.843). Almost equal gender distribution was noted among the left and right colon cancer groups. Age at diagnosis was similar among all participants, with a mean of 59.87 ± 12.35 years in the RCC group and 59.82 ± 11.19 years in the LCC group (p=0.789).

Surgical intervention was aborded electively in most cases (85.7%); however, the remaining (14.3%) cases had to be operated urgently, especially in the LCC group (6 patients *vs.* only 2 cases in the RCC group) (p=0.389). All cases benefited of lymph nodes removal with a mean of 78.6% of total cases having more than 12 lymph nodes removed (p=0.962). Large bowel obstruction was a common complication of CC, recording 19.3% of total cases with a higher incidence in LCC, 24.2% *vs.* 12.5% in RCC (p=0.267). Furthermore, perforation was only reported in 1 case (1.8%) as a presenting symptom of a left-sided tumor (p=0.390) (Table 4) [9].

Table 4: Baseline characteristics by tumor location in colon cancer.

Variable	RCC n=24 (42.1%)	LCC n=33 (57.9%)	p-Value
Gender			

Male	11 (45.8%)	16 (48.5%)	0.843
Female	13 (54.2%)	17 (51.5%)	
Age at diagnosis, mean ± SD (years)	59.87 ± 12.352	59.82 ±11.193	0.789
Family history	3 (12.5%)	1 (3.0%)	0.167
Obstruction at presentation	3 (12.5%)	8 (24.2%)	0.267
Perforation at presentation	0 (0.0%)	1 (3.0%)	0.39
Type of surgery			
Elective	21 (91.3%)	27 (81.8%)	0.318
Emergent	2 (8.7%)	6 (18,.2%)	

Regarding the tumor staging, in right-sided colon cancer, we had 7 (30.5%) patients with stage II and 16 (69.5%) patients with stage III, whereas in left-sided colon cancer, we had 9 (27.3%) patients with stage II and 24 (72.7%) patients with stage III (p=0.954). Concerning the tumor size, RCC recorded larger sizes, 5.53 cm *vs.* 4.89 cm for the LCC, but this difference is not statistically significant (p=0.252).

The median number of lymph nodes removed in the RCC group was 17 *vs.* 15 in the LCC group (p=0.786) (Table 5).

Table 5: Pathological characteristics of the tumor.

Variable	**RCC n=24 (42.1%)**	**LCC n=33 (57.9%)**	**p-Value**
Tumor size, mean ± SD (mm)	5.539 ± 2.1741	4.894 ± 1.3481	0.252
Staging			
Stage II	7 (30.5 %)	9 (27.3%)	0.954
Stage III	16 (69.5%)	24 (72.7%)	
Grading			
Grade I	3 (13.0%)	5 (15.2%)	0.932
Grade II	19 (82.6%)	26 (78.8%)	
Grade III	1 (4.3%)	2 (6.1%)	
Number of lymph nodes removed, mean ± SD	20.43 ± 12.284	18.64 ± 9.874	0.786
Number of lymph nodes positive, mean ± SD	1.61 ± 1.901	2.36 ± 2.074	0.093

In our study, 31 patients were treated with FOLFOX regimen and 26 patients with XELOX. Despite cancer localization, FOLFOX was the main regimen used for stage III CC, while XELOX was the main one for stage II (p=0.575). 19 (61.3%) patients receiving FOLFOX regimen developed serious toxicities versus 11 (42.3%) patients in the XELOX group (p=0.153).

Dose reduction, due to drug side effects, was needed for 15 patients overall (26.3% of the cases); with FOLFOX accounting for the majority of them (11 cases, 35.5%, p=0.072). Moreover, one patient treated with XELOX had to definitely stop the treatment, while in the FOLFOX group treatment cessation was needed for 6 patients (p=0.123).

Concerning Oxaliplatin-neuropathic long-term toxicity, 45.2% of the patients who underwent the FOLFOX regimen had a grade 1, 2, or 3 toxicity *vs.* 30.7% among the XELOX group; with the majority of grade 3 cases (12.9%) arising from the FOLFOX group (p=0.192) (Table 6).

Table 6: Treatment options and side effects.

Variable	FOLFOX n=31 (54.4 %)	XELOX n=26 (45.6%)	p-Value
Tumor site			
RCC	10 (41.7%)	14 (58.3%)	0.1
LCC	21 (63.6%)	12 (36.4%)	
Staging			
Stage II	8 (25.7%)	8 (32%)	0.575
Stage III	23 (74.3%)	17 (68%)	
Serious toxicities during treatment	19 (61.3%)	11 (42.3%)	0.153
Dose reduction needed	11 (35.5%)	4 (15.4%)	0.072
Treatment discontinuation	6 (19.4%)	1 (3.8%)	0.123
Neuropathy at end of treatment (%)			
No	17 (54.8%)	18 (69.2%)	0.192
Grade 1	6 (19.4%)	3 (11.5%)	
Grade 2	4 (12.9%)	5 (19.2%)	
Grade 3	4 (12.9%)	0 (0.0%)	

Patients' FU revealed 16 recurrence (28.1%) with the highest rate of recurrence observed in LCC (30.3% *vs.* 25.0 % in RCC, p=0.893) and in stage III (23.21% *vs.* 5.35% in stage II, p=0.503).

Finally, the survival rate in the RCC group was 100% in the first year post-surgery (p=0.385), remained 100% in the second year and until the sixth year (p=0.214; p=0.005 respectively), then decreased to 95.65% in the seventh year (p=0.021). However, the survival rate in the LCC group was 96.8% in the first year post-surgery (p=0.385), then decreased gradually to 93.5% in the second year (p=0.214); it reached 71% in the fifth year (p=0.005) and remained the same in the 3 years that followed.

DISCUSSION

CC is a common malignancy worldwide and a major factor of morbidity and mortality. In this study, a group of 57 patients (52.6% female *vs.* 47.4% male) with a median age of 58 years, diagnosed with CC, underwent a tumor resection procedure followed by Oxaliplatin-based adjuvant chemotherapy. 28.6% of patients had stage II *vs.* 71,4% with stage III. This difference is expected because, based on the NCCN guidelines, patients diagnosed with stage III and only high-risk stage II benefit from adjuvant chemotherapy.

54.4% of the patients were treated with FOLFOX regimen *vs.* 45.6% with XELOX. To our knowledge, there is no guidelines on which regimen to choose in treating early-stage CC. However, patient monitoring and FU, especially in our society, is easier when patients are given intravenous drugs (FOLFOX) in the hospital, rather than when patients take tablets (XELODA) at home with all the side effects that can develop.

Dose reduction, due to drug side effects (mainly to the Oxaliplatin-neuropathic toxicity), was needed for 15 patients overall (26.3% of cases). The survival rate of the total population was analyzed yearly and showed that 98.15% of the patients stayed alive after one year of surgery. This percentage decreased to 94.44% in the third year, and to 81.48% in the seventh year. Compared to the literature, the 6-year OS was approximately 78.5% in stage II-III CC after surgery and Oxaliplatin-based adjuvant chemotherapy. This emphasizes the favorable prognosis of early stage CC in terms of 5-years OS.

Many studies reported a difference between left and right colon cancer concerning physiopathology, histology, presentation and prognosis. This dissimilarity led to the use of different treatment strategies for left and right stage IV KRAS wild-type colon cancer. This option is not yet available for early stage CC.

In this study, left-sided tumors were more common than right-sided ones (57.9% *vs.* 42.1%), with almost equal gender distribution and age at diagnosis. Compared to other studies, LCC is more common than RCC, but with female predominance and older patients in right-sided CC.

Concerning survival, 10 patients passed away, with 1 patient in RCC and 9 in LCC. Accordingly, the RCC group had better prognosis than the LCC group. The 5-year survival rate is 100% in right-sided colon cancer, whereas it is 71% in left-sided ones.

This finding is inconsistent with the literature. According to Javier et al., stage III LCC patients have better prognosis than RCC. Furthermore, a study done by Nesrine et al., found a better 5-year OS in patients with LCC (78% *vs.* 42% in RCC). In addition, according to Jennifer et al., stage II colon cancer patients with left-sided tumor have worse outcome than those with right-sided one, whereas stage III RCC patients present higher mortality rate.

Moreover, Peng J et al., found that patients with stage III LCC taking XELOX adjuvant chemotherapy had better 3-year OS than those with RCC.

The difference in results between this study and previous studies can be related to the higher incidence of large bowel obstruction in LCC 24.2% *vs.* 12.5% in RCC in our population; as it is proved that obstruction at diagnosis holds a worrisome prognosis.

We must not miss the idea of the need for a larger sample size, given that the one used in this study is small (57 patients), making it difficult to statistically compare right and left-sided colon cancer. Additionally, the maximal follow-up duration of seven years may be insufficient for adequate evaluation of colorectal cancer's survival; given that it is a type of malignancy that carries a good prognosis when discovered at early stages.

For this reason, the data should be followed up and statistically assessed in few more years.

On the other hand, our results raise the question of whether treating colon cancer without taking consensus molecular subtypes into consideration may affect the prognosis. Thus adequate management and treatment guidance must be based on genetic profiling of each and every colon cancer patient.

Limitations

Our study aims to assess the outcome of a long-term regimen. Thus, due to shortage of time, we had to conduct our study in a retrospective manner, and consequently, we were forced to rely on others for accurate medical record; this may have resulted in missing information.

Furthermore, one of our major limitations is not knowing the molecular characteristics of the tumor. To detect the disease's recurrence, exams and imaging had to be done by the patient, such as CT scan, MRI, or PET scan. Unfortunately, some patients were not compliant; this led to information bias due to loss to follow-up.

We must not forget, that some of the collected information were gathered by calling either the patient or his/her family, this may have also resulted in inaccurate data.

At last, despite the need for a larger sample size to obtain more significant results, this study helped in broadening our knowledge regarding one of the most commonly encountered cancers in Lebanon.

CONCLUSION

Colon cancer is the third most common cancer among men and women. It is a type of malignancy that carries a good prognosis when discovered at early stages. The survival rate of the total population was analyzed yearly and showed that 98.15% of patients stayed alive after one year of surgery. This percentage decreased to 94.44% the third year, and to 81.48% the seventh year.

Colon cancer is divided into right and left colon cancer, which manifests with distinct physiopathology, histology, presentation, and prognosis

A better prognosis was noted in RCC compared to LCC in early stage disease (stage II-III), with a 5-year survival rate of 100% in RCC against 71% in left-sided ones. Consequently, the tumor location should be taken into consideration for the prognosis of colon cancer.

Thus, adequate management and treatment guidance must be based on genetic profiling (CMS) of each and every colon cancer patient.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the ethical guidelines outlined in the World Medical Association's Declaration of Helsinki. The study design was approved by the ethics committee of "Notre Dame Des Secours Hospital." The requirement for informed consent was waived by the ethics committee due to the retrospective nature of the study.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the archive of the hospital Notre dame des secours but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the medical director.

COMPETING INTERESTS

The authors declare no competing interests.

FUNDING

Not applicable.

AUTHORS' CONTRIBUTIONS

All the authors have contributed equally in the study design, data analysis, and writing. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

CyN wrote the main manuscript text. MM reviewed the entire research and proposed some correction. SH did the statistics for the study. CaN helped in writing the manuscript and was attentive to the smalll details. CR helped with the bibliography, figures and references.

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